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Antenatal corticosteroid therapy for fetal lung maturation

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Abstract
The research findings indicate that respiratory distress syndrome (RDS) is recognized as the leading cause of newborn death, posing a substantial challenge, particularly for preterm babies. RDS is caused by a lack of pulmonary surfactant production and the immaturity of the lungs. As per the 2019 publication released by the International Federation of Gynecology and Obstetrics (FIGO), the utilization of antenatal corticosteroids has demonstrated a 50% reduction in the occurrence of RDS, resulting in a diminished likelihood of intraventricular hemorrhage, necrotizing enterocolitis, and neonatal mortality. The use of corticosteroids in women at risk of premature labor between 24- and 34-weeks' gestation was first recommended in 1994 by the National Institutes of Health (NIH), after careful consideration on the safety and efficacy of the administration of antenatal steroids. The administration of corticosteroids usually is performed between 24- and 34-weeks' gestation. However, under circumstances it may be beneficial even at 23 weeks and at 35-36 weeks of gestation. The evidence to date is clearly against the routine administration of multiple antenatal steroid courses. In special clinical situations, a second course of betamethasone may be justifiable.

Keywords: Respiratory distress syndrome (RDS), national institutes of health (NIH), hemorrhage

Introduction
Based on the International Classification of Diseases, 10th revision established by the World Health Organization (WHO), a preterm birth (PTB) is characterized as an occurrence occurring within the gestational period of 22 to 37weeks, which corresponds to a duration of 154 to 259 days [1]. Roughly 66% of premature deliveries are linked to spontaneous preterm uterine contractions, which can occur independently or in combination with preterm rupture of membranes. Meanwhile, one-third of the remaining instances are deemed medically necessary due to various maternal, fetal, or placental irregularities. These conditions include but are not limited to preeclampsia, abnormalities in the uterus, multiple pregnancies, restricted fetal growth, fetal anomalies, placenta previa, as well as disorders within the placenta accreta spectrum. It is worth noting that preterm infants often face complex medical challenges, and the probability of encountering complications tends to increase as the baby is born prematurely. This emphasizes the importance of understanding the underlying factors contributing to premature births and the significance of early detection and intervention in such cases. Furthermore, addressing the risk factors associated with preterm deliveries is crucial in improving maternal and neonatal outcomes, highlighting the necessity for comprehensive prenatal care and risk assessment protocols. One of the most beneficial approaches amidst the numerous prenatal medications involves administering antenatal corticosteroids (ACS) through injections to expedite the process of fetal lung maturation, thereby enhancing respiratory outcomes and reducing the risk of complications associated with preterm birth [2].
Pregnant women in their 24th to 34th week of gestation who are at risk of preterm labor within the subsequent 7 days should be given antenatal corticosteroid medication. As pregnant women approach the peri viable stage, a crucial period characterized by a substantial increase in the chances of neonatal survival, it is prudent to involve their family members in the decision-making process concerning the use of corticosteroids. This collaborative decision-making should take into account the preferences of the family regarding resuscitation interventions for the newborn infant. Additionally, it is essential to take into consideration the geographical limitations on fetal viability when determining the most appropriate gestational age for initiating prenatal corticosteroid treatment.

This requires an in-depth analysis of local data related to the rates of neonatal survival and the associated health complications stemming from premature birth [3].

Infants delivered between 34 and 36 weeks of gestation, falling into the category of late preterm births, are at a higher risk of encountering negative respiratory and other consequences when contrasted with infants born at or after 37 weeks of gestation. Despite this, there is uncertainty surrounding the effectiveness of corticosteroid therapy administered to late preterm infants in improving outcomes within this specific population [4].

The existing body of research suggests that there is a decrease in the occurrence of severe respiratory illness in newborns as a result of maternal steroid therapy. Nevertheless, the absence of comprehensive long-term outcome studies within this particular patient cohort has resulted in an ambiguous assessment of the long-term safety of corticosteroids. Infants who are born prior to 39 weeks of gestation are at an increased risk of experiencing adverse respiratory outcomes in the neonate, with this risk increasing as the gestational age at birth decreases. It is worth noting that infants who are delivered through a cesarean section are particularly susceptible to adverse respiratory outcomes, especially if the delivery occurs before the onset of labor. As a result, it is not recommended to opt for prelabor elective delivery before 39 weeks of gestation unless there is confirmation of fetal lung maturity [5].

The evaluation of respiratory morbidity risk in planned cesarean births for term infants is of utmost importance when considering the possible advantages of prenatal steroids in comparison to postponing delivery till 39 weeks of gestation. In cases when a prelabor cesarean surgery is considered required during the gestational period of 37 to 38 weeks, it is advisable to provide parents with information on the benefits associated with a single administration of prenatal corticosteroids. These advantages include a decrease in the risk of RDS. The temporal aspect of cesarean delivery has a crucial role in determining the outcomes of infants, hence carrying substantial significance in the realm of public health. As per the guidelines set forth by the American College of Obstetricians and Gynecologists (ACOG), it is advised to refrain from elective delivery prior to reaching 39 weeks of gestation [6].

Guidelines for corticosteroid treatment

The advice for administering corticosteroids during pregnancy applies to all pregnant women between the ages of 24 and 34 weeks who are at risk of giving birth prematurely during the following 7 days [7].

The ideal dosage and method of delivery

According to the National Institutes of Health, there are two commonly recommended regimens for the administration of prenatal corticosteroids. The first treatment protocol is the administration of two intramuscular doses of betamethasone, each containing 12 mg, with a 24-hour time gap between each dosage. The second treatment protocol consists of four administrations of dexamethasone, each weighing 6 mg and delivered intramuscularly, with a 12-hour interval between each dosage [7].

It is not recommended to schedule several courses of prenatal corticosteroids due to concerns about potential injury to the mother and fetus, as well as the need to carefully consider the risks and benefits. According to the 2000 Consensus Panel of the National Institute of Child Health and Human Development, there is evidence suggesting that repeated courses may have potential benefits, specifically in terms of reducing the occurrence and severity of respiratory distress. However, certain studies conducted on animals and humans have expressed concerns regarding potential negative impacts on fetal development. The aforementioned issues encompass the effects on brain myelination, pulmonary development, and the functionality of the hypothalamic-pituitary-adrenal axis. Hence, it is not now advised to engage in regularly planned repeat courses or serial courses beyond a duration of two [8].

Neonatal development limitation can complicate pregnancies

There is a lack of consensus on the effects of corticosteroid therapy on intrauterine growth restriction (IUGR). Significantly decreased rates of RDS, intraventricular hemorrhage (IVH), and perinatal mortality have been observed in large cohort studies, in contrast to tiny randomized clinical trials that did not demonstrate any reduction in newborn morbidity. Therefore, it is imperative to customize the administration of steroids for these individuals based on their specific circumstances. When selecting a singular round of steroid therapy, it seems that any marginal reduction in birth weight found following several cycles of treatment in these individuals is alleviated. Furthermore, the advantages of maternal steroids in babies with limited fetal development surpass any potential negative consequences. When women exhibit signs of preterm labor, it might be advantageous to take into account cervical length measures and evaluate fibronectin/PAMG1 levels. The use of these strategies can effectively mitigate the occurrence of avoidable hospitalization and the utilization of tocolytic medicines and/or prenatal steroids [9].

For pregnancies carrying more than one foetus

Considering the improved results observed in singleton pregnancies, it is advisable that all patients between 24 and 34 weeks of gestation who are at risk of preterm delivery within 7 days, regardless of whether they have multiple pregnancies, should be administered a single course of prenatal corticosteroids, unless there are specific reasons to avoid it [10].

Regarding Diabetic Women

There is no evidence to suggest that diabetes mellitus is contraindicated for prenatal corticosteroid therapy in relation to fetal lung maturation. Nevertheless, it is crucial that women who have impaired glucose tolerance or diabetes and are undergoing prenatal steroid treatment are administered supplementary insulin in accordance with a predetermined protocol and maintain vigilant surveillance [11].

Expected Delivery

If the family has decided to resuscitate the infant in pregnancies occurring before 24 weeks with a risk of premature birth, the use of corticosteroids should be considered. The determination of the minimum gestational age for giving corticosteroids for lung maturation is significantly influenced by the local criteria of fetal viability. It is crucial to acknowledge that even in circumstances with abundant resources, the rate of intact survival is quite low [12].

Late Preterm

Pregnant women classified as late preterm, with gestational ages ranging from 34 to 36 weeks and an additional 6 days, who are at danger of birth within the next 7 days and have not previously undergone corticosteroid treatment, may potentially derive advantages from a singular administration of corticosteroids. Studies indicate that this therapy decreases the occurrence of

illness in newborns within this population. Nevertheless, it is imperative to acknowledge the lack of extensive research guaranteeing the safety of corticosteroid utilization in this particular situation [13].

Period of gestation

It is recommended to consider administering a single course of corticosteroids in situations where elective termination of pregnancy is necessary, and labor does not occur between 37 weeks and 38 weeks plus six days of gestation. This approach aims to reduce the likelihood of RDS in patients who have not previously undergone corticosteroid therapy. Cesarean deliveries carry a greater risk of worse respiratory outcomes than vaginal births, especially when cesarean delivery is conducted prior to the initiation of labor. The ACOG recommends refraining from elective cesarean sections before to 39 weeks of gestation because to the strong association between the date of delivery and infant outcomes, which carries substantial implications for public health [6].

Action mechanism

Glucocorticoids exert their effects throughout the body, especially in placental and fetal tissues, due to the presence of glucocorticoid receptors in almost all human cells, resulting in pleiotropic effects. Glucocorticoids trigger a series of actions that involve regulating gene expression, transcription, and protein synthesis when they attach to these receptors. It is crucial to acknowledge that this series of occurrences necessitates a certain amount of time, usually hours, before the consequences become evident [14].

In the context of endogenous corticosteroids, it is observed that the fetus undergoes a period of reduced glucocorticoid levels during the early and mid-gestational stages. During pregnancy, a multifaceted process of organ development begins, resulting in an increase in both maternal and fetal glucocorticoids towards the end of pregnancy. This helps the transition from being within the uterus to being outside the uterus. Betamethasone and dexamethasone principally exert their effects on the lungs by stimulating the generation of surfactants. Nevertheless, these chemicals also exert an impact on a multitude of additional organs, such as the heart, brain, hypothalamus, kidneys, and thyroid. The corticosteroids in question replicate the inherent increase in endogenous corticoids and elicit fetal adaptations that commonly manifest during the latter stages of gestation [15].

The development of the fetal lung occurs in a series of five different phases, namely embryonic, pseudo glandular, canalicular, terminal sac, and alveolar. During the gestational period spanning from 28 to 35 weeks, there is a notable augmentation in both the quantity and development of alveoli. The emergence of lamellar bodies, which function as reservoirs for surfactant, typically occurs between 22 to 24 weeks of gestation [16]. The surfactant is of utmost importance in the stabilization of alveoli through the reduction of surface tension. The substance is an intricate amalgamation consisting of lipids and apoproteins [17].

The administration of ACS therapy accelerates the development of type 1 and type 2 pneumocytes and initiates the activation of pulmonary beta receptors. As a result, it triggers changes in the structure of alveoli, the development of blood vessels, the creation of surfactants, and the removal of fluid from the airspace. A mixture of transcriptional and post-transcriptional pathways is employed to enhance surfactant production, resulting in increased synthesis of phosphatidylcholine and fatty acids in the fetal lung. The established range for the efficacy of ACS administration is commonly acknowledged to be from 2 to 7 days, a period first defined by Liggins and subsequently corroborated by additional studies, including a Cochrane review that highlighted a reduction in the occurrence of RDS among neonates who received ACS within the preceding 2 to 7 days [1].

The classification and dosage of corticosteroids

The transfer of ACS from the maternal to the fetal compartment via the placenta is crucial for the advantageous impact on fetal lung development. The degree to which medications pass through the placenta varies significantly, both among different substances and across different stages of pregnancy. The diversity in fetal lung maturation between beta- and dexamethasone is the reason for choosing these two steroids, as there have been no notable changes in fetal lung maturation between them. Prominent treatment protocols often involve the administration of a cumulative dosage of 24 mg, which can be divided into two doses of 12 mg intramuscularly (IM) for betamethasone or four doses of 6 mg IM for dexamethasone. The use of these dosage regimens guarantees the occupation of a maximum of 80% of corticosteroid receptors, hence eliciting a strong corticosteroid receptor response in the fetus. Furthermore, the augmentation of betamethasone dosage above these thresholds does not result in an improvement in its effectiveness. Nevertheless, it is crucial to acknowledge that a reduced frequency of corticosteroid administration may be associated with an elevated susceptibility to necrotizing enterocolitis, therefore warranting avoidance [18].

Effects of corticosteroids on the children in both the short and long term

The administration of ACS to women with singleton or multiple pregnancies before to PTB has the potential to interfere with the functioning of endogenous stress hormones, as cortisol is recognized as the principal stress hormone. Hence, this intervention might have both immediate and enduring consequences [19]. The solitary administration of ACS has been associated with immediate negative consequences, such as postnatal hypoglycemia. However, it is important to note that this course of treatment might also result in enduring deleterious effects, such as diminished fetal development [20] or consistent documentation of low academic achievement has been observed exclusively in cases where frequent administration of ACS has been observed. Furthermore, findings from a population-based research carried out in Finland have demonstrated a noteworthy correlation between exposure to ACS and the development of mental and behavioral abnormalities in the kids [21].

The administration of several courses of ACS, such as a second dosage or weekly doses subsequent to an initial course, has been linked to a reduction in fetal growth, suggesting a systemic impact on the baby. At the age of five, infants who experienced ACS and were born beyond 37 weeks of pregnancy showed a significant rise in neurosensory impairment, while having normal development elsewhere [20]. The findings of research conducted by the National Institute of Child Health and Development indicate a potential correlation between repeated ACS courses and a higher incidence of cerebral palsy at 2-3 years of age. However, no other abnormalities were seen during the experiment. A thorough examination was conducted to assess the risks and advantages of multicourse ACS for preterm labor, taking into account the gestational age. The findings indicate that in instances where premature delivery is expected before 29 weeks of gestation, administering a repeat course of ACS is advantageous. Nevertheless, with a duration of 29

weeks, the prevalence of enduring adverse consequences, such as inadequate growth and delay in neurodevelopment, need meticulous deliberation [22].

Rescue Dosage

Based on the guidelines provided by the WHO, in cases where preterm delivery does not transpire within a period of 7 days subsequent to the administration of the initial corticosteroid regimen, and a subsequent identification of a new risk of birthing, the possibility of initiating a new corticosteroid cycle may be contemplated [23]. According to the ACOG, it is recommended that pregnant women who are less than 34 weeks of gestation get a further course of corticosteroids if a new risk of preterm delivery emerges within one week following the original cycle. However, it is important to note that at least 14 days have passed since the initial course [6].

ACS have exhibited notable clinical efficacy and cost-efficiency in the prevention of respiratory problems in neonates. Patients who are pregnant and exhibit clinical symptoms indicative of preterm labor should be subjected to a thorough evaluation, which should include evaluations of the uterine cervix and levels of fibronectin. Corticosteroid administration should be limited to instances when there exists a robust clinical indication of premature birth during the next two to seven days [24].

Conclusion

Usually, corticosteroids are given throughout the period of 24 to 34 weeks of pregnancy to enhance the development of the fetal lungs. Nevertheless, there exist some circumstances in which their utilization may provide advantageous outcomes, such as during the 23-week and 35-36-week stages of gestation. Although there is now no evidence to justify the usual use of repeated prenatal steroid regimens. The administration of a second dosage of betamethasone may be deemed appropriate in certain clinical scenarios.

Conflict of Interest

Not available

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Not available

References

1. Dagklis T, Sen C, Tsakiridis I, Villalaín C, Allegaert K, Wellmann S, *et al*. The use of antenatal corticosteroids for fetal maturation: clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation. Journal of Perinatal Medicine. 2022;50:375-85.
2. Dagklis T, Tsakiridis I, Papazisis G, Athanasiadis A. Efficacy and safety of corticosteroids' administration for pulmonary immaturity in anticipated preterm delivery. Current Pharmaceutical Design. 2021;27:3754-61.
3. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews; c2006.
4. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, *et al*. Antenatal Betamethasone for women at risk for late preterm delivery. New England Journal of Medicine. 2016;374:1311-20.
5. Tita AT, Landon MB, Spong CY, Lai Y, Leveno KJ, Varner MW, *et al*. Timing of elective repeat cesarean delivery at term and neonatal outcomes. New England Journal of Medicine. 2009;360:111-20.
6. ACOG. Committee Opinion No.677: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstetrics & Gynecology; c2016, 128.
7. Monteiro VP, Cima LC, Tauile MT. Antenatal Corticosteroid. In: Moreira de Sá RA, Fonseca EBd, editors. Perinatology: Evidence-Based Best Practices in Perinatal Medicine. Cham: Springer International Publishing; c2022. p. 627-30.
8. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ; c2016, 355.
9. Magann EF, Haram K, Ounpraseuth S, Mortensen JH, Spencer HJ, Morrison JC. Use of antenatal corticosteroids in special circumstances: a comprehensive review. Acta Obstetricia et Gynecologica Scandinavica. 2017;96:395-409.
10. Bulletin P. Practice Bulletin No. 171: Management of Preterm Labor. Obstetrics & Gynecology; c2016, 128.
11. Monteiro VP, Cima LC, Tauile MT. Antenatal Corticosteroid. Perinatology: Evidence-Based Best Practices in Perinatal Medicine; c2022. p. 627-30.
12. Opinion C. Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstetrics & Gynecology; c2017, 130.
13. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, *et al*. Antenatal betamethasone for women at risk for late preterm delivery. New England Journal of Medicine. 2016;374:1311-20.
14. Van der Laan S, Meijer OC. Pharmacology of glucocorticoids: beyond receptors. European Journal of Pharmacology. 2008;585:483-91.
15. Hillman NH, Kallapur SG, Jobe AH. Physiology of transition from intrauterine to extrauterine life. Clinics in Perinatology. 2012;39:769-83.
16. Rubarth LB, Quinn J. Respiratory development and respiratory distress syndrome. Neonatal Network. 2015;34:231-8.
17. Jobe AH. The amazing premature lung. American Journal of Perinatology; c2019, 36.
18. Khandelwal M, Chang E, Hansen C, Hunter K, Milcarek B. Betamethasone dosing interval: 12 or 24 hours apart? A randomized, noninferiority open trial. American Journal of Obstetrics and Gynecology. 2012;206:201.e1-.e11.
19. Jobe AH. Quality improvement and antenatal steroids. The Journal of Pediatrics. 2021;232:9-10.
20. Braun T, Sloboda DM, Tutschek B, Harder T, Challis JR, Dudenhausen JW, *et al*. Fetal and neonatal outcomes after term and preterm delivery following betamethasone administration. International Journal of Gynecology & Obstetrics. 2015;130:64-9.
21. Räikkönen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. JAMA. 2020;323:1924-33.
22. Zephyrin LC, Hong KN, Wapner RJ, Peaceman AM, Sorokin Y, Dudley DJ, *et al*. Gestational age–specific risks vs benefits of multicourse antenatal corticosteroids for preterm labor. American Journal of Obstetrics and Gynecology. 2013;209:330.e1-.e7.
23. Organization WH. WHO recommendations on interventions to improve preterm birth outcomes; c2015.
24. Di Renzo GC, Cabero Roura L, Facchinetti F, Helmer H, Hubinont C, Jacobsson B, *et al*. Preterm Labor and Birth

Management: Recommendations from the European Association of Perinatal Medicine. The Journal of Maternal-Fetal & Neonatal Medicine. 2017;30:2011-30.

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